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The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection

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The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection.

Background. While an understanding of the epidemiology and clinical course of HIV-associated nephropathy (HIVAN) is growing, little is known about the risk factors and clinical course of the other renal diseases that may also occur as a complication of HIV infection. This study was undertaken to compare HIVAN to the spectrum of other kidney diseases seen among HIV-infected patients.

Methods. This retrospective cohort study included all HIV-infected patients who underwent renal biopsy during the course of their clinical care at six major medical centers. Demographic and clinical information were abstracted from each patient's clinical record. Time to initiation of renal replacement therapy was compared for patients with lesions other than HIVAN to patients with HIVAN using Cox proportional hazards regression.

Results. Eighty-nine patients (47 with lesions other than HIVAN and 42 with HIVAN) were available for inclusion. Patients with lesions other than HIVAN were less likely to be black (37/47 vs. 42/42, $P = 0.02$), more likely to have a positive hepatitis B surface antigen (10/37 vs. 4/42, $P = 0.04$), less likely to have the diagnosis of hypertension (24/46 vs. 31/42, $P = 0.03$), more likely to have a greater creatinine clearance at time of biopsy (60.6 vs. 39.0 cc/min, $P = 0.008$), and have a greater CD4 lymphocyte count at time of biopsy (287 vs. 187 cells/mL, $P = 0.04$) compared to patients with HIVAN. Lesions other than HIVAN were associated with a longer time to initiation of renal replacement therapy compared with HIVAN (HR 0.33, 95% CI 0.15-0.71, $P = 0.005$). Other factors associated with a longer time to renal replacement therapy included higher creatinine clearance at time of biopsy, greater $CD4^+$ lymphocyte count, the absence of hepatitis C antibody, and the use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The type of renal disease (HIVAN vs. other) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy ($P = 0.0001$ and 0.006, respectively). Among patients with lesions other than HIVAN, the presence of nondetectable HIV-1 RNA was not associated with a greater risk of progression of renal disease (HR 0.27, $P = 0.24$). Among patients with HIVAN, because all patients had detectable virus at the time of institution of renal replacement therapy, this highly significant association could not be quantified. Among patients with lesions other than HIVAN, the use of antiretroviral therapy was not associated with the progression to renal replacement therapy (HR 3.29, $P = 0.06$). Among patients with HIVAN, the use of antiretroviral therapy was associated with a slower progression to renal replacement therapy (HR 0.24, $P = 0.03$).

Conclusion. Among HIV-infected patients with renal disease other than HIVAN, viral suppression and the use of antiretroviral therapy are not associated with a beneficial effect on renal function; thus, additional therapeutic strategies may need to be utilized. Because renal histology is associated with prognostic differences, these data provide outcomes information that will improve the clinical utility of renal biopsy among HIV-infected patients with renal disease.

HIV-related renal diseases are the third leading cause of end-stage renal disease (ESRD) among African Americans aged 20 to 64 years [1]. While the most common histologic lesion seen among HIV-infected patients with renal disease is HIV-associated nephropathy (HIVAN), a glomerulopathy demonstrating focal segmental glomerulosclerosis with collapsing features, a spectrum of other histologic lesions occurs with almost an equal cumulative frequency [2]. These lesions include amyloidosis, minimal change disease, cryoglobulinemia, and various forms of immune-complex glomerulonephritis, such as IgA nephropathy, membranous nephropathy, and

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membranoproliferative glomerulonephritis [2–18]. While an understanding of the epidemiology and clinical course of HIVAN is growing, little is known about the risk factors and clinical course of the other renal diseases that may also occur as a complication of HIV infection.

Based on estimates that renal histologies other than HIVAN may account for between one third and one half of the cases of renal disease among HIV-infected patients [2, 18], an understanding of their risk factors and clinical course is imperative to further investigation into prevention and treatment strategies. This study was therefore undertaken to establish a better understanding of the clinical epidemiology and course of the spectrum of renal diseases that complicates HIV infection. The risk factors, clinical course, and potential modifying factors, including $CD4^+$ count, HIV-1 RNA level, and the use of antiretroviral medications will therefore be examined among the spectrum of renal diseases that complicates HIV infection.

METHODS

The retrospective cohort study included all HIV-infected patients who underwent renal biopsy during the course of their clinical care as determined by their treating nephrologists at Indiana University School of Medicine, Mount Sinai School of Medicine, Wake Forest University, Emory University, MetroHealth Medical Center (Cleveland), and Duke University Medical Center between January 1, 1995 and January 1, 2001. This study was approved by the Institutional Review Board of each institution. Because of the study design and methods, the Institutional Review Board at each institution waived the requirement for consent. Therefore, no patient was contacted, all information was abstracted directly from the medical record, and data were collected without the ability to subsequently link it back to the individual.

Data collection

Demographic and clinical information at baseline were abstracted for each patient from their clinical record to include gender, age, race, risk behavior for HIV acquisition, hepatitis C antibody status, hepatitis B surface antigen status, and the presence of either diabetes mellitus or hypertension. Risk behavior for HIV acquisition was coded as related to sexual activity versus intravenous drug use (IVDU) among those patients in whom the information was available. Diabetes mellitus was defined as the presence of glucose intolerance requiring dietary or pharmacologic management. Hypertension was defined by the use of antihypertensive medications at the time of renal biopsy.

Information reflecting the clinical course of each patient's renal disease was also abstracted from the medical record for each available clinical encounter from the time of renal biopsy until the last available clinical encounter. This information included weight, blood pressure, laboratory studies of serum creatinine, $CD4^+$ lymphocyte count, HIV-1 RNA level, and the presence of proteinuria, and medication use of antiretroviral therapy, prednisone, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB). HIV-1 RNA was coded as detectable or nondetectable based on the threshold of the HIV-1 RNA assay utilized to allow comparison between assays and among centers. Events such as the institution of renal replacement therapy or death and the date of their occurrence were noted.

The kidney biopsy reports were obtained for each patient and were examined by two investigators (T.A.F. and L.A.S.). All of the biopsies sampled renal cortex (mean glomeruli/biopsy 21.7 $\pm$ 10.6; median 20; range 5 to 59). Eleven of the biopsies had no glomeruli available for immunofluorescence microscopy; one biopsy had no glomeruli available for electron microscopy. Biopsies were coded as HIVAN based on the presence of diagnostic features described by D'Agati et al [19]. Where patients had features of both HIVAN and another pathologic process [i.e., membranous or immune complex glomerulonephritis, not otherwise specified (NOS)], the biopsies were coded to reflect the presence of HIVAN.

Data analysis

Creatinine clearance was calculated using the Cockcroft-Gault formula [20]. The demographics and laboratory parameters were described for the cohort overall and for groups of patients defined by their histologic diagnosis (i.e., HIVAN vs. lesions other than HIVAN). Clinical and demographic differences between groups were compared using the chi-square and Student *t* test for categorical and continuous variables, respectively. Where data were markedly skewed, the Wilcoxon rank-sum test was used.

Renal survival distributions for groups based on histologic diagnosis were estimated using the Kaplan-Meier methodology, using initiation of renal replacement therapy as the event. If the patient did not require renal replacement therapy, renal survival was censored at time of last known follow-up or death. Survival distributions were compared in univariate analysis using the log-rank test.

The associations between clinical and demographic variables listed in Table 1 (including academic center and year of biopsy) and time to initiation of renal replacement therapy were estimated using Cox proportional hazards regression. The relationships between disease progression and clinical factors such as $CD4^+$ lymphocyte

Table 1. Patient characteristics at time of kidney biopsy

	HIVAN	Non-HIVAN lesions	*P* value
Number of patients	42	13 Immune complex GN 8 Membranous nephropathy 6 Diabetic glomerulopathy 5 Membranoproliferative GN 5 Hypertensive nephrosclerosis 3 Interstitial nephritis 2 Amyloid 1 FSGS without HIVAN 1 Minimal change disease 1 Acute renal failure related to indinavir 1 IgA nephropathy 1 Chronic pyelonephritis	
Gender F/M	7/35	9/38	0.76
Age *years*[a]	41.7 (1.42)	43.0 (1.04)	0.46
Race			
White	0	2	0.02
Black	42	37	
Hispanic	0	7	
Native American	0	1	
Risk factor			
Sexual	12	11	0.22
IVDU	11	20	
Hepatitis C antibody status			
Positive	17	25	0.08
Negative	24	16	
Hepatitis B surface antigen status			
Positive	4	10	0.04
Negative	38	27	
Hypertension			
Present	31	24	0.03
Absent	11	23	
Diabetes mellitus			
Present	6	11	0.28
Absent	36	36	
Systolic blood pressure *mm Hg*[a,b]	133 (5)	134 (5)	0.92
Diastolic blood pressure *mm Hg*[a,b]	81 (3)	81 (3)	0.94
Creatinine *mg/dL*[a]	4.7 (0.7)	2.6 (0.4)	0.006
Creatinine clearance *mL/min*[a]	39.0 (5.3)	60.6 (5.8)	0.008
Use of antiretroviral therapy[b]			
Yes	11	16	0.42
No	31	31	
Use of ACEI/ARB[b]			
Yes	6	10	0.39
No	36	37	
HIV-1 RNA level[a,b]	196,137 (48,513)	146,044 (46,488)	0.46
HIV-1 RNA detectable			
No	5	5	
Yes	37	42	0.85
$CD4^+$ lymphocyte count[a,b]	187 (29)	287 (38)	0.04
Days of follow-up	457.6 (68.8)	682.4 (78.5)	0.04
Outcomes			
Renal replacement therapy (RRT)	25	17	0.06
Death prior to institution of RRT	4	4	
Censored at end of follow-up	13	26	
Year of biopsy			
1995	4	1	0.04
1996	3	4	
1997	4	9	
1998	8	13	
1999	8	15	
2000	11	5	
2001	4	0	

NOS, not otherwise specified; GN, glomerulonephritis.

[a]Expressed as mean (standard deviation).

[b]These summary values represent patient information obtained at the time of biopsy. Values for laboratory parameters and use of these medications were collected and incorporated into the analysis as they varied over the course of the disease and were added or discontinued in subsequent clinical visits and are included in the survival analyses.

count, HIV-1 RNA level, and the use of different classes of medications (antiretroviral medications, ACEI, ARB, prednisone), systolic blood pressure, and diastolic blood pressure were examined as time-varying covariates. This allowed the relationship between these clinical and laboratory parameters and outcomes to be estimated as these values vary over the clinical course of the HIV infection. Creatinine clearance at time of biopsy was forced into the model to control for differences in renal function at time of entry into the cohort (i.e., at time of biopsy). The proportional hazards assumption was tested for each of the variables in the final model. No evidence for violation of the proportional hazards assumption was demonstrated.

Clinically significant interactions between histologic diagnosis (i.e., HIVAN compared with lesions other than HIVAN) and HIV-1 RNA level, $CD4^+$ lymphocyte count, hepatitis C infection, and the use of antiretroviral medications and ACEI or ARB on the time to initiation of renal replacement therapy were prespecified in the design phase of the study and tested in separate models. Where interactions were significant, multivariable analyses were repeated to estimate the association between those variables and outcome among patients with HIVAN and lesions other than HIVAN separately.

Survival models were built similarly using the combined end point of initiation of dialysis or decline in creatinine clearance to below 15 ml/min to account for patients whose renal function declined to a level justifying the initiation of renal replacement therapy [21], but who opted against it or died prior to initiation.

The decision to compare outcomes among patients with HIVAN to patients with all lesions other than HIVAN was made in the design phase of this study to address the clinical utility of renal biopsy in a population where HIVAN is the lesion identified in significant frequency. Following the completion of data collection, based on the inclusion of patients with kidney disease felt by the investigatory team to be unlikely related to HIV infection (such as diabetes mellitus and hypertension), additional sensitivity analyses were performed, excluding those patients to test the stability of results.

All analyses were performed using the intent-to-treat approach (i.e., patients were analyzed according to the treatment they were prescribed regardless of compliance). All P values were reported as two-sided, and all CIs reported were 95% intervals. All analyses were performed using Stata (version 8.0, College Station, TX, USA).

RESULTS

Eighty-nine patients were identified for inclusion. Forty-two patients had HIVAN on renal biopsy. Those patients with lesions other than HIVAN included 13 patients with immune complex glomerulonephritis (NOS), eight patients with membranous glomerulopathy, six patients with diabetic nephropathy, five patients with membranoproliferative glomerulonephritis, five patients with hypertensive nephrosclerosis, three patients with interstitial nephritis, two patients with amyloid, and one patient each with FSGS without HIVAN, minimal change disease, acute renal failure related to indinavir, IgA nephropathy, and chronic pyelonephritis.

In general, patients with lesions other than HIVAN were similar to patients with HIVAN at time of biopsy in terms of gender, age, risk behavior for HIV acquisition, the presence of diabetes mellitus, measures of systolic and diastolic blood pressure, use of medications, including antiretrovirals and ACEI/ARB, and HIV-1 RNA level (Table 1). Patients with lesions other than HIVAN were less likely to be black (37/47 vs. 42/42, $P = 0.02$), more likely to have a positive hepatitis B surface antigen (10/37 vs. 4/42, $P = 0.04$), less likely to have the diagnosis of hypertension (24/46 vs. 31/42, $P = 0.03$), more likely to have a greater creatinine clearance at time of biopsy (60.6 vs. 39.0 mL/min, $P = 0.008$), and have a greater CD4 lymphocyte count at time of biopsy (287 vs. 187 cells/mL, $P = 0.04$) compared to patients with HIVAN. Patients with lesions other than HIVAN trended toward being more likely to be infected with hepatitis C (25/41 vs. 17/41, $P = 0.08$).

Twenty-seven patients with HIVAN and 32 patients with lesions other than HIVAN received antiretroviral therapy during the period of follow-up ($P = 0.71$). The time to initiation of antiretroviral therapy was similar for both groups (169 ± 249 compared with 128 ± 201 days for patients with and without HIVAN, respectively, $P = 0.49$). Creatinine clearance at time of initiation of antiretroviral therapy was greater in patients with lesions other than HIVAN (69 ± 41 mL/min) compared to patients with HIVAN (41 ± 32 mL/min) ($P = 0.006$), there were no differences in CD4 lymphocyte count and HIV RNA level between groups at the time of antiretroviral initiation (223 ± 267 vs. 249 ± 243 cells/mL, $P = 0.21$, and $132{,}429 \pm 185{,}644$ vs. $59{,}249 \pm 108{,}587$ copies/mL, $P = 0.31$ for patients with HIVAN and patients with lesions other than HIVAN, respectively).

Seventeen of 47 patients with lesions other than HIVAN [six with immune complex glomerulonephritis (NOS), two with membranous nephropathy, four with diabetic nephropathy, two with membranoproliferative glomerulonephritis, two with hypertensive nephrosclerosis, and one with interstitial nephritis] required the institution of renal replacement therapy at an average time of 731 days ($\pm$ 642 days) from renal biopsy. Twenty-five of 42 patients with HIVAN required the institution of renal replacement therapy at an average time of 254 days ($\pm$331 days) from renal biopsy ($P = 0.0003$ comparing time to initiation of renal replacement therapy). There was no difference in last available creatinine clearance

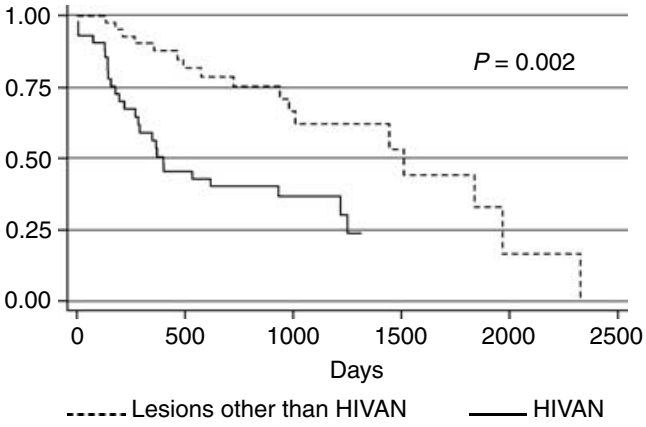

Fig. 1. Time to initiation of renal replacement therapy from time of renal biopsy among patients with HIV-associated nephropathy (HIVAN) and with lesions other than HIVAN.

Table 2. Multivariable model of associations between clinical and demographic variables and time to initiation of renal replacement therapy among the entire cohort[a]

	HR	95% CI	*P* value
Lesions other than HIVAN vs. HIVAN	0.33	(0.15–0.71)	0.005
$CD4^+$ lymphocyte count (per increase in 10 cells/mL)	0.99	(0.99–0.99)	0.01
Creatinine clearance (at time of biopsy)	0.98	(0.97–0.99)	0.004
Hepatitis C Antibody	2.60	(1.26–5.37)	0.01
ACEI/ARB	0.41	(0.17–0.96)	0.04
HIV-1 RNA (nondetectable vs. detectable)	0.16	(0.02–1.18)	0.07

[a]The type of renal disease (HIVAN vs. other) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy ($P = 0.0001$ and 0.006, respectively).

prior to the institution of dialysis between groups with and without HIVAN (13.5 ± 12.9 compared with 11.1 ± 6.0 mL/min, $P = 0.78$). Unadjusted survival curves demonstrated better renal survival among patients with lesions other than HIVAN compared to patients with HIVAN (Fig. 1, $P = 0.002$).

In the fully adjusted model, lesions other than HIVAN were associated with a longer time to initiation of renal replacement therapy compared with HIVAN (HR 0.33, 95% CI 0.15-0.71, $P = 0.005$) (Table 2). Other factors associated with a longer time to renal replacement therapy included greater $CD4^+$ lymphocyte count (HR 0.99 per increase in 10 cells/mL, $P = 0.01$) and higher creatinine clearance at time of biopsy (HR 0.98 per 1 mL/min increase, $P = 0.004$). The presence of hepatitis C antibody was associated with a faster time to institution of renal replacement therapy (HR 2.60, $P = 0.01$). The use of an ACEI or ARB was associated with a longer time from renal biopsy to institution of renal replacement therapy (HR 0.41, $P = 0.04$). A nondetectable HIV-1 RNA viral load was associated with a trend toward a longer time from biopsy to institution of renal replacement therapy (HR 0.16, $P = 0.07$).

The type of renal disease (HIVAN vs. lesions other than HIVAN) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy ($P = 0.0001$ and 0.006, respectively), indicating that the risk of progression to the initiation of renal replacement therapy associated with both HIV-1 RNA level and the use of antiretroviral therapy were different among patients with HIVAN and patients with lesions other than HIVAN. The fully adjusted models were estimated separately among patients with lesions other than HIVAN and among patients with HIVAN. Among patients with lesions other than HIVAN, a nondetectable HIV-1 RNA was not associated with a longer time to initiation of renal replacement therapy (HR 0.27, 95% CI 0.03-2.4, $P = 0.24$). Among patients with HIVAN, all patients had detectable virus at the time of institution of renal replacement therapy. Because no patient with HIVAN had nondetectable levels of HIV-1 RNA when they reached this event, this highly significant association could not be quantified.

Among patients with lesions other than HIVAN, the use of antiretroviral therapy was not associated with the progression to renal replacement therapy (HR 3.29, 95% CI 0.93-11.16, $P = 0.06$). Among patients with HIVAN, the use of antiretroviral therapy was associated with a slower progression to renal replacement therapy (HR 0.24, 95% CI 0.07-0.84, $P = 0.03$).

A sensitivity analysis using time to initiation of dialysis as the end point, and excluding the 17 patients with kidney disease related to diabetes mellitus, hypertension, interstitial nephritis, FSGS (not HIVAN), acute renal failure related to indinivir, and chronic pyelonephritis also revealed similar results in terms of direction and significance (HR 0.34 for lesions other than HIVAN as compared with HIVAN, 95% CI 0.14-0.82, $P = 0.02$). In models excluding these patients, the type of renal disease (HIVAN vs. lesions other than HIVAN with stated exclusions) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy ($P = 0.0001$ and 0.01, respectively). Among patients with lesions other than HIVAN, the presence of nondetectable HIV-1 RNA was not associated with a longer time to initiation of renal replacement therapy (HR 0.49, 95% CI 0.05-5.05, $P = 0.55$). Among patients with lesions other than HIVAN, the use of antiretroviral therapy was not associated with the progression to renal replacement therapy (HR 5.12, 95% CI 0.90-29.2, $P = 0.07$).

When initiation of dialysis or decline in renal function below a creatinine clearance of <15 mL/min was considered as a composite end point for the entire cohort, similar results in terms of direction and significance were demonstrated (HR 0.41 for lesions other than HIVAN as compared with HIVAN, 95% CI 0.20-0.85, $P = 0.02$). The type of renal disease (HIVAN vs. lesions other than

HIVAN) interacted significantly with HIV-1 RNA level and the use of antiretroviral therapy ($P = 0.0001$ and 0.008, respectively). Among patients with lesions other than HIVAN, nondetectable HIV-1 RNA was not associated with a longer time to initiation of renal replacement therapy (HR 0.30, 95% CI 0.04-2.63, $P = 0.28$). Among patients with lesions other than HIVAN, the use of antiretroviral therapy was not associated with the progression to renal replacement therapy (HR 2.25, 95% CI 0.69-7.35, $P = 0.18$).

Due to advanced disease, six biopsies designated as HIVAN did not have all classic histologic features of HIVAN well documented. In a final analysis, these biopsies were recoded as FSGS (non-HIVAN). There was no change in the direction, magnitude, or significance of these results (data not shown).

DISCUSSION

This study describes the epidemiology and clinical course of the spectrum of HIV-related kidney diseases. Patients with HIVAN and lesions other than HIVAN are similar with respect to demographics and clinical characteristics, with the exception of race and the presence of hepatitis B and C infection. All patients with HIVAN were black, while the group of patients with lesions other than HIVAN included some white and Hispanic patients. Additionally, patients with lesions other than HIVAN were more likely to have concurrent infection with either hepatitis B or C. HIVAN compared with lesions other than HIVAN was associated with a shorter time to the initiation of renal replacement therapy controlled for differences in renal function at baseline. Coinfection with hepatitis C, a decreased $CD4^+$ lymphocyte count, and the use of ACEI/ARB were also significantly associated with a faster time to renal replacement therapy, while the association between HIV-1 RNA level and outcomes demonstrated a trend that did not reach conventional levels of statistical significance. Lastly, the beneficial associations between a nondetectable HIV-1 RNA level and the use of antiretroviral agents on the progression of renal disease seen among patients with HIVAN was not present among patients with lesions other than HIVAN.

To our knowledge, this is the first study to document the clinical course of a moderate number of patients with lesions other than HIVAN exploring modifying factors. This study is consistent with previous case reports of patients with membranous nephropathy in which therapeutic benefit was derived from medications other than antiretrovirals (e.g., predisone) [14, 15]. Our findings are, however, inconsistent with a smaller cohort of HIV-infected patients with renal disease published recently [12]. Of the 23 patients included, only 12 underwent renal biopsy. While no patient who received antiretroviral therapy experienced a doubling of serum creatinine or the progression to ESRD, the small number of patients available for inclusion, and the limited information regarding histology of renal lesions, limits the power and conclusions that may be drawn from this study. Similarly, case reports of a patient with membranous nephropathy and immune-complex nephropathy demonstrate a reduction in proteinuria [13, 22] and stable renal course [22] temporally related to changes in antiretroviral regimen that resulted in reduction in HIV-1 RNA levels. Small sample size and limited follow-up also limit the conclusions that may be drawn from these case reports.

Sentinel studies in both humans and animal models provide evidence for HIVAN resulting from a direct viral infection of cells of the kidney such as the glomerular epithelial cells [23–26]. Little information is available, however, on the pathobiology of renal diseases in the HIV-infected patient other than HIVAN. Four HIV-infected patients with immune-mediated proliferative glomerulonephritis were previously examined, revealing both circulating and in situ HIV-1 antigen-specific immune complexes present in renal biopsy tissue [9]. Similar findings were present in a study of two HIV-infected patients with IgA nephropathy [8]. While it is unclear if lesions such as membranous glomerulopathy have similar HIV-related immune mediation, these data suggest that treatment focused entirely on suppressing the production of such immune complexes through suppression of viral replication using antiretroviral therapy may not confer substantial benefit. Immunosuppressive therapies to affect the inflammatory response to these complexes at the level of the kidney should be tested as potential treatment strategies, with a focus on developing treatments that may be safely administered in this already immunosuppressed population.

While this study presents data regarding outcomes among patients with renal diseases other than HIVAN, it is not without limitation. Because this study utilizes observational data reflecting the clinical care setting, the importance of bias introduced through the selection of patients for biopsy, and the use of various agents, including antiretroviral therapy and ACEI/ARB, must be stressed. Bias may be introduced by selection for those patients with symptoms resulting in the detection of renal disease, referral to a nephrologist, and selection for biopsy. This bias may affect generalizability to patients whose renal disease differs from patients presented herein with respect to characteristics at time of biopsy. Given that limited available information on clinical course has been published, clinical practice guidelines supporting uniform indications for biopsy are not available. This limitation should therefore be considered in generalizing these results to all HIV-infected patients with kidney disease. These data may however be utilized to generate hypotheses to be tested in prospective evaluation.

Additionally, factors such as anticipated compliance may affect the use of antiretroviral therapy and other

therapies, such that there may be factors that affect outcomes that result in a decision to minimize or withhold antiretroviral use by a patients' HIV care provider. There were also differences between groups with respect to renal function at time of biopsy. While this may reflect a more rapid decline in renal function among patients with HIVAN, the possibility of patients with lesions other than HIVAN having improved access to healthcare cannot be ruled out. These biases may impact conclusions. The impact of histology on the decision to begin antiretroviral therapy should also be considered. While there were no differences between groups with respect to use of antiretroviral therapy at biopsy or during the course of follow-up, time to initiation of antiretroviral therapy relative to biopsy, or CD4 lymphocyte count or HIV RNA level at time of initiation of antiretroviral therapy, it should be noted that patients with lesions other than HIVAN had a greater creatinine clearance at time of initiation of antiretroviral therapy similar to that seen at time of biopsy. The impact of histology on the decision to begin antiretroviral therapy and, subsequently, outcomes is not clear. However, arguably, this provides patients with lesions other than HIVAN greater time exposure toward having the use of antiretroviral therapy affect outcomes if that relationship were present.

Further, patients who were lost to follow-up before their initiation of dialysis may have introduced informative censoring in this study. While the outcomes of death and the censoring event of end of observation are balanced between groups, the potential impact of this cannot be assessed. Because information on nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, intercurrent morbid events, and ongoing smoking or drug abuse was not specifically collected, their impact on outcomes cannot be assessed. Finally, while this does represent the largest cohort available for study, the limitations of sample size must be stressed. While the associations between both HIV-1 RNA level and antiretroviral medications demonstrated elsewhere [27–32] among patients with HIVAN were seen in this study, the failure to find significant associations between these variables and outcomes among patients with lesions other than HIVAN may represent a type II statistical error. Further examination of these relationships is essential to determine if no such similar associations between HIV-1 RNA level and antiretroviral medications and outcomes exist among patients with lesions other than HIVAN, or if they are merely attenuated as compared with the associations seen among patients with HIVAN.

CONCLUSION

Given the survival benefit conferred by antiretroviral therapy among patients with HIV-infection, the use of antiretroviral therapy is indicated independent of its ability to positively affect secondary complications of HIV infection, such as renal disease. Arguably, the non-HIVAN renal diseases represent a spectrum of disease with significant heterogeneity of pathobiology that is incompletely understood. This heterogeneity may be associated with the inconsistencies in the response of these lesions to antiretroviral therapy. These data suggest that antiretroviral therapy and suppression of viral replication may not confer the same benefit to renal disease to patients with lesions other than HIVAN, as demonstrated in observational studies among patients with HIVAN [27, 28, 29, 32]. Given the overall mortality benefit of, and subsequent indication for, antiretroviral therapy [33], this may not impact the decision to begin antiretroviral therapy in the HIV-infected patient regardless of the presence of type of renal disease. However, these data suggest that among HIV-infected patients with renal disease other than HIVAN, the use of antiretroviral therapy is not associated with the same beneficial effect on the associated kidney disease. Additional therapeutic strategies may need to be utilized, including immunosuppression with prednisone and other agents. For patients with declining renal function, knowledge of their renal histology would provide powerful prognostic information that would alter therapy in the appropriate clinical circumstances. Practically, these data provide outcome information to increase the clinical utility and potentially frequency of renal biopsy among HIV-infected patients with renal disease.

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